ARCHIVES OF DISEASE IN CHILDHOOD

Vol. 9. DECEMBER, 1934. No. 54.

CONTENTS

ISSUED BY THE BRITISH MEDICAL ASSOCIATION.

London: British Medical Association House,

Tavistock Square, W.C.1.

Yearly Subscription (6 numbers), 25/- *Single Number, 4/6*

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THE UREA CLEARANCE TEST IN CHILDREN

BY

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The value of the urea clearance test in the estimation of renal function is now well established. It was thought advisable before using it as a routine at this hospital to check the normal response in children with that of the adult and to compare the results of the test with the one previously in use (McLean's urea concentration test). The increase in the minute volume of the urine as a result of applying the surface area correction is considerable and might well invalidate results based on adult values. A good discussion of the underlying principle of the test is given by Peters and van Slyke[1] but a brief mention of it is made here.

It has been found that if the kidneys are excreting more than a certain volume per minute (the augmentation limit—about 2 c.c. in the adult) the amount of urea excreted bears a constant ratio to the blood urea irrespective of the volume of the urine. Thus with a constant blood urea a constant amount of urea is excreted every minute. In other words a constant volume of blood may be conceived as giving up all its urea. This volume of blood is calculated to be 75 c.c. per minute, and is the 'maximal clearance value' in the adult.

If the kidneys are excreting less than this volume of urine, it is found that the amount of urea excreted is affected by the volume of urine as well as by the blood urea, and it has been found that the quantity of urea varies approximately as the square root of the minute volume of the urine. Thus if 75 c.c. of blood are cleared with a minute volume of 2 c.c. then $75 \times \frac{\sqrt{1}}{\sqrt{2}}$ c.c. (53·1 c.c.) of blood should be cleared with a minute volume of 1 c.c. Experimentally 54 c.c. is found to be the average value and this figure is taken as the 'standard clearance value' for the standard of comparison whenever the minute volume fails to exceed 2 c.c.

It is obvious, however, that both the blood and urine volume will vary with the size of the subject and a correction depending on the surface area is used so as to bring the excretion rate into comparison with the normal.

In performing the test it is more satisfactory to obtain the maximum clearance value. This is not always possible but the standard clearance value can always be determined. The maximum value is obtained by giving a dose of urea and large quantities of fluids some two to four hours before starting the collection of urine. At an accurately noted time the subject empties the bladder and at the end of about one hour the bladder is again emptied and the time noted. All the urine passed in this period is kept and measured. Blood for urea determination is taken as near the middle of the period as possible. A second hour period with a second blood urea is advisable.

In obtaining the standard value no preliminary preparation is required. The urine is collected as above and the blood urea estimated. It is not usually necessary to take a second blood test since no variation occurs in our experience within one hour unless urea or much fluid had been taken previously. The only precaution in the preparation of the patient is the avoidance of diuretics in the previous meal such as tea, coffee or alcohol. The height and weight of the subject must be taken accurately.

For the analysis we have used Archer's urease method[2] for blood and McLean's modification of the hypobromite method[3] for urine. As a check the urease method for urine has been used but no differences of clinical importance between the two methods were found.

Calculation.—The surface area is first obtained, either from tables or from Du Bois' formula: $A = H^{0.735} \times W^{0.425} \times 71{\cdot}84$, where A = surface area in sq. cm., H = height in cm. and W = weight in kgm. The average adult surface area is taken as 1·73 sq. metres.

The corrected urine minute volume (Vc) is found thus:—

$$Vc = \frac{\text{Volume of urine passed per minute}}{\text{Surface area in sq. metres.}} \times 1{\cdot}73$$

If the value of Vc is above 2 the 'maximum clearance' (M) is found from the following formula:—

$$M = \frac{\text{mgm. urea per 100 c.c. urine}}{\text{mgm. urea per 100 c.c. blood.}} \times Vc$$

The average for adults is 75.

If the value of Vc is under 2 the 'standard clearance' (S) is obtained as under:—

$$S = \frac{\text{mgm. urea per 100 c.c. urine}}{\text{mgm. urea per 100 c.c. blood.}} \times \sqrt{Vc}$$

The average for adults is 54.

In practice it is convenient to express results as a percentage of the corresponding average value. Most normal cases fall between 80 per cent. and 120 per cent. A considerable variation can be expected and indeed is normal, but consecutive results below 80 per cent. can be taken in the adult as abnormal.

Results.

Thirty-nine children suffering or convalescent from diseases not involving the renal tract were examined. The urine was tested and was normal in all but one patient who was passing albumin. He was a patient with haemophilia with no history of renal involvement. Table 1 gives a summary of the results expressed as percentage of the adult normal. It is apparent from this that the average for children is higher than that for the adult and also that the zone into which most cases fall is also greater (80–140 as against 80–120). Inasmuch as once the kidney has passed the minimal threshold it is regarded as normal, the upper limit has no great clinical interest, and since the lower limit coincides with the adult value it has not been deemed advisable to use a different normal for children.

In examining the results applied to individual cases no normal case failed to exceed in at least one test the minimal value, but one subject gave four results—all ' standard ' values, three of which were below 80 per cent., and this must be considered to be a ' doubtful ' result.

TABLE 1.

Percentage of adult normal.	Standard.	Maximal.
	Number of Cases.	
Below 80	8	2
80-99	20	8
100-119	29	7
120-139	19	11
140-159	7	4
160 or over	13	9
Average percentage	119	128
Average clearance value, c.c. ...	64	97

McLean's test was applied to the same group and in all but one values over 2·5 per cent. urea were obtained in one or more specimen indicating a normal function. In the one failure the highest value was 2·4 per cent. and this was the case of haemophilia referred to above. Both tests thus give a satisfactory response with the normal.

TABLE 2.

Disease.	Standard.	Maximal.	McLean.
Ac. haemorrhagic nephritis ...	N	—	N
,, ...	N	—	N
,, ...	D	D	N
,, ...	D	A	N
,, ...	D	A	N
,, ...	A	A	N
,, ...	A	A	A
Bismuth nephritis	A	A	N
Chronic nephritis	A	A	A
,, ...	A	—	D
Pyelonephritis	N	N	N
Bilateral hydronephrosis	A	A	N
Pyelitis and nephrectomy ...	D	A	N

N = Normal, D = Doubtful, A = Abnormal.

Another group of thirteen children suffering from some disease involving the kidney were examined by each test. The results are summarized in table 2. It will be seen that in this small series of pathological cases the agreement between the results ceases to be good. There is no great difference between the two clearance tests, but in three cases doubtul results according to the ' standard ' test are definitely abnormal in the ' maximal ' test. McLean's concentration test gives normal results in six cases in which the maximal test gives an abnormal response. It is apparent therefore that the capacity of the kidney to excrete urea decreases earlier in disease than the capacity to concentrate urea in the urine.

While admitting that the numbers are small the results are so definite that the conclusion may be drawn that the urea clearance test is more likely to detect early loss of kidney function than is McLean's concentration test. Brief mention may be made of three applications of this method.

Effect of anaesthetics.—Six subjects who were not suffering from renal or septic conditions were examined by the maximal clearance test as soon as possible after an anaesthetic had been given. Ether and nitrous oxide were used in all cases and the duration was from ten to thirty minutes. The blood urea was found to be raised but the clearance was normal. Repeated in ten days time all the tests were normal including the blood urea. The conclusion may be drawn that the post-operative rise in blood urea is not due to failure of renal excretion.

Nephrectomy.—Two patients have been examined after nephrectomy. The first case four months after the operation gave a normal concentration test but failed to give a normal maximal clearance test. It was thought that perhaps the remaining kidney had not hypertrophied sufficiently to be able to clear as much blood urea as two normal kidneys while still being able to concentrate urea. The kidney was removed for chronic pyelitis and was functioning before removal. The second kidney was only slightly infected but may not have been quite normal. The second patient was examined two weeks after the operation and gave a normal maximal clearance. The kidney was removed for sarcoma and possibly had been relatively functionless for some time before its removal.

'Nephrosis.'—A good example of this syndrome was examined by both the clearance techniques and by McLean's method. It was not possible to get a sufficient flow of urine to pass the augmentation limit but the standard clearance was normal as also was the concentration test.

Summary.

The renal function in two groups, one normal and the other pathological, has been examined by the maximal and standard clearance tests and by the urea concentration test. No difference was found between the results of the different methods in the normal group but in the pathological group the results differed. The order of sensitivity was: maximal clearance, standard clearance, urea concentration.

The effect of anaesthetics (ether-nitrous oxide) has been examined. No change in the kidney function was detected.

Our thanks are due to the honorary medical and surgical staff of the Hospital for Sick Children for permission to investigate children under their care.

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CUTANEOUS MYIASIS IN INFANTS

BY

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AND

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Sufficient interest is attached to the occurrence of cutaneous myiasis in infants to warrant the publication of the report of three cases of this clinical entity.

Case reports.

Case 1.—K. E., a male, aged three weeks, was admitted on June 9, 1934, and discharged on June 20, 1934.

COMPLAINT. Rash on arm and neck for one day.

HISTORY OF PRESENT ILLNESS. The infant was quite well until the day of admission, when spots appeared on the arms and neck. The baby had been sleeping out of doors.

PHYSICAL EXAMINATION revealed a well-developed and well-nourished male infant who was not acutely ill. The cutaneous system showed the presence of what appeared on first examination to be several scattered pustules on the right arm and on the right side of the neck. From the area on the right side of the neck a small maggot was removed with forceps. A definite small purulent sinus was left, surrounded by a red, indurated margin. This sinus in the side of the neck is shown in fig. 1.

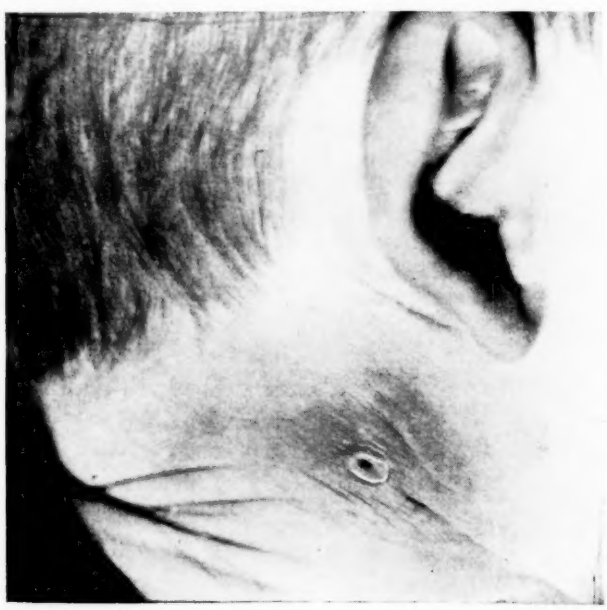

FIG. 1.—Case 1.

Case 2.—P. P., a female aged three, was admitted on June 14, 1934, and discharged on June 18, 1934.

COMPLAINT. Red spots resembling bites under eye and behind the ear for two days.

HISTORY OF PRESENT ILLNESS. The baby was in good health until two days prior to admission, when two red spots appeared under the eye and one behind the ear. They resembled bites and were swollen. From each of these areas several small maggots were extracted. This infant also had been sleeping out of doors.

PHYSICAL EXAMINATION revealed the same type of lesion as in the last patient (fig. 2).

FIG. 2.—Case 2.

Case 3.—R. G., a male aged five weeks, was admitted on June 22, 1934, and discharged on June 25, 1934.

COMPLAINT. Rash on left arm for one day.

HISTORY OF PRESENT ILLNESS. The baby was perfectly well until the day before admission. It was noticed that there were several small 'mosquito bites' on the left arm. The left hand began to swell, became red, and pus discharged from these areas which now appeared like 'boils.' Little maggots were seen wriggling in the centre of these spots. As in the previous cases, the infant had been sleeping out of doors.

PHYSICAL EXAMINATION revealed an acutely swollen left lower arm (fig. 3) and oedematous hand with twelve or more lesions resembling furuncles. From thirty to forty larvae were removed. Some lesions contained as many as six larvae.

Comment.

The skin infestation in these three infants is due to the deposition of the larvae of a species of fly known as Wohlfahrtia vigil (Walk.). The occurrence of this fly as a human parasite was first reported in 1920 from two cases by E. M. Walker[1]. The same author described two more cases in 1922[2], and gives a summary of eight cases in different parts of Canada in 1931[3]. In the last article the author briefly describes the characteristics and habits of the fly. The larvae are discharged directly on the skin surfaces of the patient by the adult gravid fly. They quickly migrate to areas where there are folds of skin, e.g. at the side of the neck and axilla, and burrow into the subcutaneous

tissue producing an inflammatory reaction. Ford[4] has made some interesting observations on the behaviour of this species of fly, and in her article discusses its life cycle and feeding habits. Patients with this infestation are young infants who have been sleeping out of doors. Most reported cases have occurred in the month of June[5, 6]. In the present series the babies were healthy, sleeping in the open air, and all skin lesions were produced in the month of June. In the observations of Ford on larviposition, she mentions the fact that the gravid fly was definitely attracted by the head

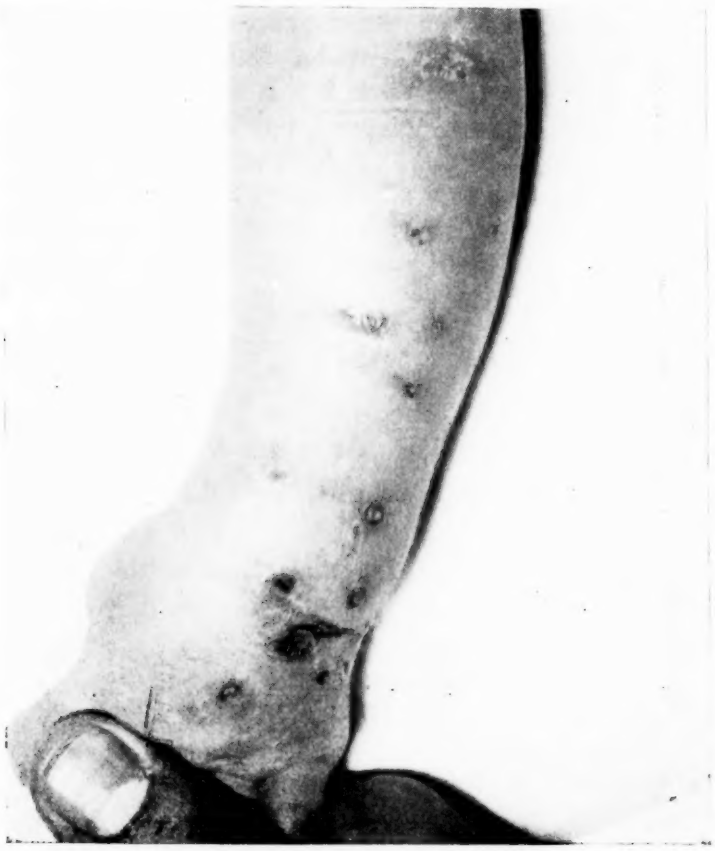

FIG. 3.—Case 3.

and face of the the rabbit used in her investigation. In the three cases cited most of the lesions occurred around the upper part of the infants' bodies. It will be noticed that in one case of the series a lesion was found on the lower eye-lid. In a search for places where the flies live, Walker states in a personal communication that they were found along railway tracks, and that the larval stage probably develops in young mammals. In the three reported cases larvae obtained were reared into adult flies by Dr. Ford, who has furnished us with the following data:—

Case 1. June 12, 1934—Larva was 13 mm. in length.
,, 15, ,, ,, pupated.
July 1, ,, Adult fly emerged.

Case 2. June 15, ,, Larvae were 5 mm. in length.
,, 16, ,, ,, ,, 10 ,, ,, ,,
,, 17, ,, ,, ,, 15 ,, ,, ,,
,, 18, ,, ,, pupated.
July 4, ,, Adult flies emerged.

Case 3. June 23, ,, Larvae were 10 mm. in length.
,, 24, ,, ,, ,, 15 ,, ,, ,,
July 2, ,, ,, pupated.
,, 9, 10 and 12, Adult flies emerged.

The treatment followed in these cases was quite simple. The larvae were removed by forceps or by pressure and the wounds dressed with moist compresses. The remaining inflammatory part of the lesions responded quickly under this treatment, disappearing in a few days. In discussion of the prevention and treatment of this condition, Walker[3] stresses the necessity for the careful screening of young infants sleeping out of doors during the summer months. He also states, ' The presence of pimple or boil-like lesions of the face, neck, chest, arms, or other parts liable to be exposed during sleep, should suggest the possibility of myiasis, in which case the larvae should be removed immediately using antiseptic precautions.'

Summary.

1. Three cases of cutaneous myiasis produced by the larvae of Wohlfahrtia vigil (Walk.) in infants are reported.

2. The lesions occurred in young healthy infants sleeping out of doors during the month of June.

3. Prevention and treatment are briefly mentioned.

The authors wish to thank Professor E. M. Walker and Dr. Norma Ford, of the Department of Biology, University of Toronto, for the information furnished on the species of fly producing this condition.

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THE HAEMATOLOGY OF INFANTILE SEPSIS*

BY

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This communication records the results of blood investigations in infantile sepsis. This condition includes numerous septic manifestations, such as skin lesions (abscesses; boils; pustules), otorrhoea, gastroenteritis, pyuria, etc., occurring soon after birth and up to end of first year. The work on this subject is comparatively new, as indeed, is infantile haematology in general, nor does literature provide any representative or systematic account of haematological investigation of mild sepsis in infancy. An attempt to elucidate this problem is made here and for this purpose the selected cases included every manifestation of sepsis in infants. The blood was obtained from the heel, provision being made to have the feet warm before commencing, and blood counts and smears were carried out at weekly intervals over a period of four to five months.

The haemoglobin level in the selected infants.

In order to make any deductions it is necessary to compare the haemoglobin level in disease with the findings in healthy infants. Average haemoglobin levels in healthy infants given in standard textbooks are numerous, and as different methods of estimation have been employed in each case, results have varied according to apparatus used, whether the prick was made at the heel or ear and on several other factors, e.g. birth weight. The higher the birth weight, the higher on an average is the haemoglobin level likely to be from one month old and during most of the first year of life.

Elvehjem, Paterson, and Mendenhall[1] in America employed the Newcomer method, which gives readings a little higher than those of Mackay, to which reference will be made later. Mackay's estimations were carried out by means of a Price-Jones–Haldane haemoglobinometer, which gives higher readings for the same absolute amount of haemoglobin in the blood than other methods used in this country. In spite of this, results by the Sahli method do not present gross differences from those of the Price-Jones–Haldane method. The method I have employed in every case has been the new Sahli method. The apparatus used was Sahli–Leitz with double comparator tubes, an accurately graduated pipette and a graduated diluting tube. The hydrochloric acid is placed in a graduated tube to mark 10. Next 20 c.mm. of blood are sucked up into the pipette and added to the

* Presented as part of a thesis for M.D. Degree of the University of Edinburgh.

acid in the graduated tube. The blood and acid are mixed by means of a stirring rod specially provided, and allowed to stand for one minute. Distilled water is then added and the colour matched with that in the graduated tubes, and reading recorded. The reading gives the per cent. of haemoglobin and the grammes of haemoglobin per 100 c.c. of blood.

Case records.

Case 1.—Artificially-fed infant, no iron treatment given. Birth weight unknown; weight at four weeks, 8 lb. 2 oz. Clinical findings:—skin sepsis, intermitten pyuria and occasional gastro-intestinal disturbance.

Age in weeks	Haemoglobin level (Sahli method) per cent.	Average haemoglobin values in the bottle-fed (Mackay's findings)[2] per cent.
4	87	
5	80	
6	75	80
6½	75	
7	75	
8	73	
9	75	69·4
10	80	

The average haemoglobin from four to eight weeks was 77 per cent. as compared with 80 per cent. in the bottle-fed series, and in the second month 77·5 per cent. as compared with 69·4 per cent.

This conclusion associates itself with the remarks of Mackay[3] when she says, 'Most slight infections, where the general health is not seriously impaired do not appear to influence the haemoglobin level. The next estimation taken after a cold in the head, an attack of bronchitis or a slight enteritis usually showed no drop which appeared attributable to the illness.'

Case 2.—Artificially-fed infant, weight at commencement of investigation, 5 lb. 8 oz., iron treatment given when ten weeks old. In this case the infant exhibited a generalized mild infection with dyspepsia, intermittent pyuria, skin sepsis, discharging ears. Despite these conditions of ill health, the haemoglobin level appeared to have been well maintained. (Detailed weekly haemoglobin levels are not quoted in each case.) The average haemoglobin level, between two and three months, was 73 per cent., as compared with corresponding 69·4 per cent. of the same age period given by Mackay, and 76 per cent. between three and four months as compared with 71 per cent.

Prematurity does not appear to have influenced the haemoglobin level as much as might be expected. According to Kunckel, Lichtenstein, Lande and others, there is a distinct and early impoverishment of the haemoglobin of the blood, which reaches its maximum about three to four months. According to Mackay the haemoglobin level in premature infants is high at birth, there is an early drop and minimum level is reached at three to four months of life. However, the above case appears to have a good haemoglobin level at three months.

Case 3.—This child was a breast-fed infant until eight to nine months. Blood investigations were commenced at age of nearly eleven months and the weight then was 13 lb. 11 oz. Clinical manifestations:—discharging ears, interstitial pneumonia, abscesses of the skin.

Age in months	Haemoglobin level (Sahli method)	Normal haemoglobin level Breast-fed (Mackay's findings)	Average haemoglobin level
	per cent.	per cent.	per cent.
$10\frac{3}{4}$	48	86	72·8
$11\frac{1}{4}$	46		
$11\frac{1}{2}$	46	86	73·1
$11\frac{3}{4}$	50		
12	53		
$12\frac{1}{2}$	55		
$12\frac{3}{4}$	55	86	73·9
13	55		
$13\frac{1}{4}$	60		
$13\frac{1}{2}$	62	86	76·4
$13\frac{3}{4}$	68		
14	68		
$14\frac{1}{4}$	68		
$14\frac{1}{2}$	69		
$14\frac{3}{4}$	70		

By ' normal haemoglobin level ' is meant the haemoglobin estimation in breast-fed babies weighing 6 lb. and upwards at birth, iron-treated from the third month onwards.

Here a profound degree of anaemia occurred at the outset; this will be referred to later. The haemoglobin level was correspondingly low and together with the septic process a change in the haematopoietic system was found. Whether sepsis produced this profound anaemia, or the anaemia was present first, and then septic infection followed, is a difficult issue, but I feel that sepsis was a causative factor in the production of the anaemia. Despite iron treatment, the haemoglobin level only gradually reached 70 per cent. The average haemoglobin levels were as follows:—

10–11 months. 48 per cent. as compared with 86 per cent. for breast-fed, iron-treated infants,
and 72·8 per cent. untreated breast-fed infants.

11–12 months. 48 per cent. as compared with 86 per cent. for breast-fed, iron-treated infants,
and 73·1 per cent. untreated breast-fed infants.

12–13 months. 55 per cent. as compared with 86 per cent. for breast-fed, iron-treated infants,
and 73·9 per cent. untreated breast-fed infants.

13–14 months. 64 per cent. as compared with 86 per cent. for breast-fed, iron-treated infants,
and 76·4 per cent. untreated breast-fed infants.

This case raises the question as to whether iron treatment has any effect in curing anaemia of septic infection. Mackay points out ' that in infants treated with iron, the haemoglobin level was raised from the third month onwards. It is possible with continuous iron to maintain a level of 77 per cent. in infancy and upwards from five to twelve months.' This refers to healthy infants. According to Parsons, in infections the beneficial effect of iron is greatly diminished or even absent. I am in agreement with the above view, for observations on septic infants, as compared with ordinary nutritional anaemias, show a poor response to iron therapy. That several factors are responsible for increase in haemoglobin level must be taken into account. When general health improves and resistence to infection is established, iron may be more efficacious in increasing the haemoglobin level.

Case 4.—Artificially-fed infant, weight at six weeks 7 lb. 12 oz. Iron treated since eleven weeks old. Presented numerous skin abscesses and respiratory complications. The average haemoglobin level between one and two months was 74·5 per cent. as compared with 80 per cent. of the bottle-fed series (Mackay). From two to three months this was 66 per cent. as compared with 69·4 per cent.; three to four months, 68·5 per cent. as compared with 70·1 per cent.

In this case, too, there appears only a small reduction from the standard given by Mackay. Indeed the haemoglobin level in this infection falls within limits of normal, bottle-fed infants. It is interesting to find that the mother's haemoglobin was 30 per cent. when the infant was seven weeks old, and that she was already receiving treatment for her profound degree of anaemia. According to the majority of authorities infants born of anaemic mothers derive from them their full complement of haemoglobin and Baar and Stransky state that anaemia of the mothers does not produce anaemia in the new-born child.

Case 5.—Artificially-fed infant, weight 5 lb. at 3 weeks. Clinical findings:—skin sepsis, discharging eyes and gastro-intestinal upset. The haemoglobin between one and two months was 70 per cent. as compared with 80 per cent. of bottle-fed series (Mackay); from two to three months 65·5 per cent. as compared with 69·4 per cent. In this case a dried milk containing extra iron was given for a period of a few weeks, and a small quantity of ferri et ammon. cit. given after this. Comparatively little difference exists between haemoglobin figures given by Mackay and those obtained in this case.

Case 6.—Artificially-fed infant, weight 6 lb. 12 oz. at five weeks. No iron treatment given. The infant failed to gain weight, showed a few skin lesions and had a mild gastro-intestinal upset. The average haemoglobin level for period one to two months was 74 per cent. as compared with 80 per cent. and two to three months 67 per cent. as compared with 69·4 per cent. (Mackay). Here, too, little divergence exists between the findings in septic infants and in normal infants.

A further group of haemoglobin estimations were taken from patients reported to have had sepsis in infancy, who had reached the age of one, two, three years.

AGE (YEARS).	HAEMOGLOBIN. PER CENT.
IN GROUP 1–2 YEARS.	
1	65
1 3/12	57
1	58
1 4/12	48
2	55
IN GROUP 2–3 YEARS.	
2 5/12	60
2 8/12	60
3	65
IN GROUP 3–4 YEARS.	
Nearly 4	67

In group one to two years, the haemoglobin is rather lower than the given standard, and if 65 per cent. be included in the normal ratio, the other cases are much reduced. In most of these cases rickets has complicated the picture, and the resultant reduction of haemoglobin may be attributable to the anaemia of rickets. Then, too, malnutrition in these cases is an important factor, since many of these children are the victims of poor circumstances and improper nutrition.

In age group two to three years, the haemoglobin level lies in the neighbourhood of 60 to 65 per cent. In second year the haemoglobin rises and should be in the neighbourhood of 70 per cent., so that here, too, there is only a slight disparity in the findings. Similarly, in group three to four years, the patient showed a level of 67 per cent., which does not really fall far short of the findings in town children living under poor conditions.

Conclusions.—The haemoglobin in mild sepsis in infancy shows little appreciable reduction from the standard laid down by Mackay for normal infants of that period. In the older group of children, the haemoglobin seems variable, being much reduced in age group one to two years, other factors such as rickets and malnutrition complicating the picture. It seems quite definite that this lowering of the haemoglobin level has no connection with the previous history of sepsis. In the group two to three years, the haemoglobin more nearly approaches the normal standard. In the group three to four years, almost normal standards have been approached.

Number of red blood corpuscles.

As a result of repeated blood counts, it is concluded that the red cells do not appear to fall below normal limits, and there is little to be learnt from this investigation alone. Its use lies in the estimation of the colour index.

The colour index.

It has been said that in infections in infancy, the colour index becomes low. Kugelmass[7] states that sepsis shows a rapidly developing anaemia with

a low colour index. In infants this fact has not come to light, the colour index being either ·8 or ·9 and in a few instances ·7. In the older infant (case 3) the colour index was low and remained at ·6 for a long period, finally reaching ·7.

Recticulocytes.

This estimation proves very variable. In some instances out of 600 cells counted, only 2 showed reticulation. In one instance only did they number between 6 and 8 per cent.

The white blood corpuscles.

There are no absolute and uniform standards for the behaviour of the white blood corpuscles in infants. It is regrettable that the whole blood picture in infancy is not of greater value than it is. So little has been known of the normal physiological reactions of the infantile blood system, and even though the behaviour of the red cells, haemoglobin and colour index are now fairly elucidated, there still remains considerable ignorance of the white cell response. The number of white blood corpuscles varies according to the time of day, from person to person, and different estimations for the normal standard have been presented for nurslings as follows (all quoted from Schilling[1]): Gundobin 9,000 to 15,000, Benjamin 8,000 to 12,000, Rominger 9,200 to 23,700, Hofmann and Welker 6,200 to 21,600, all of which constitute an extreme range of figures. All cell counts were done at corresponding times on different days and ranged between 7,000 and 12,000.

The differential count.—The most valuable information is to be obtained from the differential count with its distribution of the neutrophil series in relation to other components of the blood film. I have consistently used Leishman's stain and counted 200 cells by the Schilling method. The Schilling haemogram and clinical picture were then correlated. In the Schilling count, the polymorph neutrophils are divided into groups according to their degree of maturity:—

1. myelocytes, 2. metamyelocytes, 3. band forms, and 4. segmental forms.

This enables one to estimate the shift to the left (Arneth) which represents an increase in metamyelocytes and band forms indicating an irritation of the bone marrow to increased activity from infection. Schilling[1], Feldman[5] Piney[6], Kugelmass and Lampe[7], Rogatz[8], Weiss[9], Schmal, Schmidt and Serebrijski[10], and others state that in infective processes the differential count shows a shift to the left, and during the phase of recovery this shift is decreased, lymphocytes are increased as well as the cosinophiles. Normal haemogram variations are wide.

During my work on the blood films I have been interested in the great number of immature forms of cells, that is, metamyelocytes and band forms, which determine the degree of shift. In a count of 200 cells it has been by no means unusual to find the existence of as many as 47 ' bands ' and in quite

a number of cases these vary between 20 and 40, these figures being very much higher than the normal standard given by other observers. Even in the blood of normal healthy infants up to the age of two years, I have been struck by the greater number of band forms as compared with the mature segmental forms. Indeed, very few polymorphs show the true segmentation, that is to say, cells showing only a mere thread of chromatin uniting the nucleoli. Consequently one is inclined to feel that the standards set by Ockel, Hofmann and Welker (quoted by Schilling[1]) are low as far as band forms are concerned. If five 'stabs' (band forms—Schuessler and Schilling) are considered pathological this would bring every nursling into the field of ill health. The blood picture of the adult reacts entirely differently and can in no way be compared with that of the child. Wide variations may occur from time to time. Schilling states that the erythrocytic and leucocytic blood picture of a child is highly labile, often responding to irritation in a disproportionate manner. It must be remembered that in artificially-nourished infants a rapid activity of the lymphocytic apparatus is developed. In most cases the reaction has been of the lymphocytic type, which is in accordance with the findings of most observers. It is often claimed that monocytes are high. One case showed 19 per cent. Piney does definitely state that a high monocyte count occurs in infancy and quite readily disappears as the blood assumes a more mature picture. The following observations were made in the course of the present investigation:—

1. On one occasion a hyperleucocytosis with the presence of 6 per cent. eosinophils occurred and this proved a rather favourable situation.

2. On quite a few occasions an increase in lymphocytes occurred during the phase of gastro-intestinal upset; this lymphocytosis was probably a defensive mechanism during the period of bowel infection.

3. A moderate or high white blood count occurred quite frequently with a marked shift, a slight decline in lymphocytes and few eosinophils, even in a phase of recovery, so that this finding cannot be regarded in an unfavourable light. However, this interpretation is not adequate unless correlated with the clinical picture.

4. At no time was there complete absence of eosinophils.

5. In some instances I have found a decreased shift and a corresponding increase in lymphocytes and eosinophils with recovery from the clinical standpoint.

6. The eosinophils appeared to be increased when the patient was putting up a resistence to infection, and would appear to be a favourable phenomenon.

Case records.

The cases are not given in detail, but sufficient notes to draw deductions are given. In each case the first and last week's blood counts are referred to. (These cases are the same series as those used for haemoglobin estimations.)

Case 1.—Age four weeks. Skin sepsis, pyuria, gastro-intestinal upset.

25.5.33. White blood cells 11,800. Marked shift to the left, 44·5 per cent. immature forms of polymorphs (metamyelocytes and band forms). Lymphocytes 40 per cent., eosinophils 2 per cent., monocytes 6 per cent.

3.7.33. In the phase of improvement the lymphocytes numbered 67·5 per cent., eosinophils 4·5 per cent., monocytes 3·5 per cent., and shift decreased showing 21 per cent. of immature forms of polymorphs. W.B.C. 10,000.

Case 2.—Premature infant. Blood investigations commenced at eight weeks old and in a phase of recovery. Skin sepsis, pyuria, gastro-intestinal disturbance and discharging ears.

19.5.33. W.B.C. 9,300. Immature forms of polymorphs 17 per cent., lymphocytes 70 per cent., eosinophils 3 per cent., monocytes 9 per cent.

17.7.33. W.B.C. 8,000. Infant on road to complete recovery. Immature forms 36 per cent., lymphocytes 58 per cent., eosinophils 1 per cent., monocytes 1 per cent. This case definitely deviates from rules laid down for the response of blood in infection; for the lymphocytes are decreased as well as eosinophils and the shift to the left is great during recovery. Premature children are supposed to have a high lymphocyte count with neutrophilia at first, this then recedes with marked neuclear shift. Several observers have declared that in the fourth week the lymphocytes range between 75 and 82 per cent. in premature infants but they do not state the behaviour of the lymphocytes at the age of two months. At no time has there been a lymphocytosis of over 70 per cent. in this case.

Case 3.—An older infant, age nearly eleven months, with septic manifestations following one another at frequent intervals. Discharging ears, abscesses of the skin, interstitial pneumonia.

26.4.33. W.B.C. 8,740. Immature forms 19·5 per cent., lymphocytes 54 per cent., eosinophils 2 per cent., monocytes 14·5 per cent. Clinically in the stage of improvement. Weekly blood count till 31.7.33 Immature forms 21 per cent. (that is a greater degree of shift to the left), lymphocytes 75 per cent., monocytes 1·5 per cent., eosinophils 1 per cent., W.B.C. 7,800.

Child considerably improved. Gained weight. Haemoglobin increased to 70 per cent. Increase in number of immature forms. Increase in lymphocytes. Eosinophils decreased to 1 per cent. The monocytes have decreased considerably from 14·5 per cent. to 1·5 per cent.

Case 4.—Infant six weeks old. Numerous skin abscesses. Respiratory involvement and occasional pyuria. W.B.C. 10,900.

2.7.33. Immature forms 33 per cent., lymphocytes 65 per cent., eosinophils 1·5 per cent., monocytes 2 per cent. Infant was in a highly infective state, losing weight, marked gastro-intestinal disturbance and skin sepsis. Weekly blood counts till 21.8.33. W.B.C. 9,300, immature forms 22 per cent., lymphocytes 68 per cent., eosinophils 7 per cent., monocytes 3 per cent. Immature forms had decreased in number, lymphocytes and eosinophils had increased and the monocytes showed no change, being in the neighbourhood of 2 per cent.

The general condition was good, and this case does apparently adhere to the rules laid down by haematologists in septic infections.

Case 5.—Aged three weeks. Unable to suck. Mild skin lesions. Discharging eyes and ears.

11.7.33. W.B.C. 40,000. Immature forms 30 per cent., lymphocytes 62 per cent., eosinophils 6 per cent., monocytes 2 per cent. Clinical condition poor.

Weekly blood count till 28.8.33. W.B.C. 17,100, immature forms 34 per cent. (shift to the left is large), lymphocytes 58 per cent., eosinophils 1 per cent., monocytes 2 per cent. Clinical condition good. Throughout the haemogram, the eosinophils were evident. This constant presence of eosinophils and the hyperleucocytosis of the first examination proved a favourable situation. In the final phase there was a good gain in weight, clear urine, the blood picture showed increased shift to the left. Lymphocytes and eosinophils were decreased.

Case 6.—Aged six weeks at commencement of blood investigations, presenting gastro-intestinal upset, peeling of skin and failure to gain weight.

22.7.33. W.B.C. 8,000, immature forms 23 per cent., lymphocytes 66 per cent., eosinophils 2 per cent., monocytes 5 per cent. Clinical picture showed a distinct improvement since admission to the hospital. Weekly blood counts till 30.8.33. W.B.C. 9,500, immature forms 15·5 per cent., (there is a much lesser degree of shift to the left), lymphocytes 74 per cent., eosinophils 3 per cent., monocytes 3·5 per cent. Infant made good progress. Weight increased from 7 lb. 3 oz. to 9 lb. Here the shift has decreased; lymphocytes and eosinophils increased, so that the response in this blood picture has been similar to that of acute infections in adults.

These six cases fall into two groups. Three have shown a typical response to sepsis as referred to in text books, and three showed atypical results. There are little in the way of normal standards for comparison, and results which may be classed as normal for adults with infection do not appear to be consistent in infants.

In examining the blood film, the reds in a great number of cases have been poorly filled, i.e., they have shown hypochromia. Some of the blood corpuscles were irregularly shaped and sized, and only in a few instances were nucleated reds and megaloblasts seen. The resultant microcytic hypochromic anaemia has been evident to a mild degree with the exception of case 3. As all these cases of sepsis were sub-acute or chronic, it seems feasible that the haemopoietic system like other tissues is likely to suffer as well from the infective process.

How do these infections produce anaemia? In mild sepsis the infection probably acts by suppressing the myeloid function, and this may be so small as to produce no apparent results in the blood. In the sub-acute and chronic infections, the rate of regeneration of haemoglobin and red blood cells may be depressed to a slight extent. Hypochromia may be regarded as due to the fact that haemoglobin saturation of the young cells is the last stage of erythropoiesis. Improvement in the general condition of the infant and of the blood picture occurred together.

Summary.

1. In infantile sepsis the haemoglobin is not reduced to any appreciable degree except in the small group of out-patients in whom rickets and malnutrition complicated the picture.

2. The colour index was between 0·8–0·9, red cells $3\frac{1}{2}$ to $4\frac{1}{2}$ millions per c.mm.; reticulocytes between 1 and 2 per cent. The white cells varied from

8,000 to 15,000 or 16,000 per c.mm., and the differential count in all cases showed a preponderence of immature forms with very few segmental or mature polymorphs in the neutrophil series.

3. In three out of six cases fully investigated there was a decrease in the shift to the left, and an increase in lymphocytes and eosinophils during the final phase of recovery. In others, the findings varied.

My sincere thanks are due to Dr. J. C. Spence of the Babies' Hospital and Mothercraft Centre, Newcastle-on-Tyne, under whom these investigations were carried out. I should also like to express my thanks to Dr. Elsie Wright and Dr. A. Ogilvie of the same Institution.

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POLLEN SENSITIVENESS IN CHILDREN WITH ASTHMA

BY

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Grass pollen is well recognized as a common cause of symptoms of allergic hypersensitivity. The frequency with which pollen sensitiveness is manifested by hay fever tends to divert attention from its importance as a factor in the causation of asthmatic attacks, except in those patients in whom hay-fever is present in addition to their asthma, or the small group who have attacks of asthma in the pollen season only. It was with the idea of attempting to find out the frequency with which pollen sensitization occurred in asthmatic children in this country that the following investigation was carried out. We have failed to trace any references in the literature which throw light on this subject.

The work was suggested by the fact that a considerable number of patients who had been having few or no attacks during the winter and early spring, apparently relapsed during May and June. Examination of the case notes of those who had been attending hospital for some time showed that this was an annual occurrence, and that whereas the attacks occurred occasionally during the winter months, a series of attacks were recorded in the early summer. Often this increase in the frequency of attacks was continued throughout the summer and only diminished in the autumn. Two hundred and fifty unselected cases attending the Asthma Clinic at the Hospital for Sick Children, Great Ormond Street, were investigated. Intradermal tests were carried out on two hundred and ten of these with a mixed pollen extract and a control solution of buffered phosphate. In addition, one hundred and forty-one were tested with a dust extract.

Preparation of extracts.

The pollen extract used was obtained by mixing the extracts of six pollens and diluting this mixture appropriately.

* Working for the Asthma Research Council with the aid of a grant from the Sir Hally Stewart Trust.

The grasses used were Timothy, Orchard, Sheep's Fescue, Meadow, Vernal, 'Yorkshire Fog.'* This mixture contained 2 mgm. of nitrogen per cent. Two dust extracts were employed. These were made by extracting dust samples obtained from the houses of asthmatic individuals who appeared to be dust-sensitive clinically. The extracting fluid used was in one case Evans' Solution, and in the other an equal quantity of buffered phosphate and glycerine. The extract obtained was passed through a Berkfeld filter and diluted ten times with Evan's Solution before use. The nitrogen contents of the two extracts were 7 and 20 mgm. per cent. respectively.

Criterion of positive reaction.

A reaction was called positive if an area of erythema with or without a wheal developed after ten minutes at the site of the injection, in the presence of a negative control. In the event of the control solution giving a reaction, as happened not infrequently among the group of cases in which eczema was or had been present, the reaction to the protein extract was only counted positive if it was definitely larger and more intense than the control.

The reaction when positive usually showed an increase in the size of the wheal by about 2–3 mm. and the flare produced measured on the average 30–40 mm. The same extract tested on cases of frank hay fever gave reactions of about the same size, but tending to be slightly larger. This method of testing is slightly more sensitive than the scratch method. The concentration of the pollen extracts used for the scratch test was approximately sixteen times as strong as that of each individual pollen in the mixed solution for intradermal use. Twenty cases were compared by testing with the scratch and the intradermal method with the following results:—

	Scratch method		Intradermal	
	Positive	Negative	Positive	Negative
Twenty cases	8	12	11	9

Results of investigation.

The 250 patients examined were subdivided into four clinical groups:—

1. Those whose asthma occurred at all seasons of the year with no special seasonal incidence.

2. Those who were worse in the summer.

3. Those who were worse in the winter.

4. Those whose symptoms had not been present for a sufficient length of time to allow classification into the above groups.

The relative proportions of these groups and their reactions to pollen and dust are shown in the following table.

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* Obtained from Messrs. Duncan & Flockhart.

	Relative proportion. Percentage of total	Percentage sensitive to pollen	Number tested	Percentage sensitive to house dust	Number tested
Non-seasonal asthmatics	33	33	66	68	47
Asthmatics worse in summer	28	61	64	85	46
Asthmatics worse in winter	32	32	68	56	43
Asthmatics of recent origin	7	50	12	80	5

From these figures there can be no doubt that grass pollen is an allergen of greater importance in the precipitation of asthmatic attacks than is generally recognized. If the total number of patients tested is taken, 42 per cent. give skin reactions to pollen. A series of thirty-three children of the same age group, not suffering from any allergic condition, attending general medical out-patients, were tested with the same extract: none of them gave any reaction.

If the asthmatic groups are subdivided according to age an increase in the number of cases giving positive reactions occurs after the age of nine years.

	2-6 yr.	6-9 yr.	9-12 yr.
Percentage of pollen sensitive cases ...	38	39	57
Number tested	55	92	51

This is in accordance with the well-recognized fact that sensitiveness to inhalants becomes more marked as childhood advances.

When sensitiveness to pollen was considered in relation to the mode of onset, the following figures were obetained:—

Mode of onset in 250 patients	Percentage of pollen sensitive cases in each group
After eczema (20 per cent.)	66
Spontaneous asthma (22 per cent.) ...	42
After bronchitis and other respiratory infections (44 per cent.)	34
After hay-fever (1 per cent.) ...	100
Miscellaneous (13 per cent.) ...	10

Thus the group who have or have had allergic eczema (20 per cent. of the series), show the highest proportion of reactors (66 per cent.). The capacity for sensitization to allergens of all types seems to be far higher in this than in any other group. For example, 42 per cent. claimed to be clinically sensitive to certain foods compared with 12 per cent. of the remainder: 22 per cent. were clinically egg-sensitive compared with 4 per cent. of the rest.

The group of apparently pure spasmodic asthma gives the next figure of 42 per cent., while those patients in whom asthma followed a respiratory infection (such as bronchitis, whooping cough, pneumonia), give 34 per cent. positive responses.

Discussion.

The seasonal variations in the frequency of attacks among asthmatics depend on a number of unrelated factors. A large proportion of children suffering from asthma are regularly found to be worse during the summer months. There are at least three factors which may be responsible for this increase in severity.

First, the actual increase in the temperature of the air appears in certain cases to favour the allergic state, possibly by disturbing the balance of sympathetic and parasympathetic tone. This factor is of particular importance in children whose vasomotor instability is well recognized. Secondly, the presence of grass pollen in the air during the summer* means that in addition to the ordinary constituents of dust, a further potent allergen is inhaled in relatively large amounts. Owing to the drier weather, the total quantity of dust in the atmosphere will also be increased. Thirdly, in the case of children there is far less restriction on their movements and activities in the fine warm weather. They are allowed to wander further afield, and owing to the extended daylight the hour at which they go to bed is delayed. This means that in many cases children of poor stamina become unduly fatigued during the summer months. Fatigue or any other factor tending to lower the general health predisposes to asthmatic attacks. It must also be remembered that naso-pharyngeal and respiratory infections are not uncommonly acquired as a result of a chill following violent exercise.

The series of tests carried out in this paper indicates that grass pollen sensitization is of greater importance than is usually recognized. Whereas 5·6 per cent. of the patients tested, claimed to have clinical hay-fever in addition to their asthma, 42 per cent. reacted to a mixed pollen extract in weak dilution. In a certain number of these it was recognized that going into fields, or ' being in the garden when the grass is mown ' brought on attacks. Many were unaware that contact with pollen was in any way responsible for attacks. This lack of clinical confirmation is so common in cases of inhalant sensitiveness as to be almost usual: very few feather-sensitive patients realise that contact with feathers is responsible for their nocturnal asthma, though quite a high proportion are improved by discarding their feather-filled bedding material.

* It is not sufficiently recognized that though the majority of grasses pollinate during the latter half of May, all June and half of July, there are several (e.g., Timothy, Creeping Bent, Dog's Tooth) that pollinate in August and September, and many hay-fever sufferers have a second period during which their symptoms recur during August and early September.

The previous failure to observe that face powder causes symptoms in cases of spasmodic rhinorrhoea among women, who are relieved at once by its omission, is a constant source of surprise. The absence of clinical confirmation of pollen sensitivity need not therefore lead us to deny its presence. Its clinical recognition is largely a question of education. Food sensitiveness is, on the other hand, in our experience far more frequently recognized by the patient.

An attempt to obtain some sort of clinical confirmation was obtained by subdividing the patients who were worse in the summer from the remainder; and it was shown that whereas 61 per cent. of the former were pollen sensitive only 33 per cent. of the latter gave positive skin reactions. It must be recognized that this is only a rough method of subdividing these patients, based entirely on the statement of the parents. Several of the patients said to be worse in the winter admitted to having more or less constant wheezing in June and July.

Two preparations of dust extract were used on many of the patients in this series, and the results obtained were in some ways surprising. The dust used was obtained from the sweepings of rooms of asthmatics: it was thought that since more time is spent by the children indoors in the winter than the summer that the percentage giving positive reactions would at least be roughly equal in the two groups. As the figures show, however, the summer group give a higher proportion of reactors (85 per cent.) than the winter group (56 per cent.), the group showing no seasonal incidence occupying a middle position (68 per cent.). This would not be surprising if the dust had been obtained from some outdoor source, in which the proportion of vegetable debris might be presumed to be greater than in house dust and present in the air in increased amounts during the summer months. As it is one is left to conclude that the summer group as a whole have a greater tendency to develop sensitization than the winter group in whom respiratory infections play a more prominent part. Moreover, it suggests that though infection of the respiratory tract may and almost certainly does predispose to development of protein sensitization, it is also responsible for development of the symptoms of asthma by other means—possibly due to reflex spasm. Further confirmation of the increased sensitivity of the summer group is found in the figures for sensitiveness to foods—32 per cent. of those worse in the summer claiming to be unable to eat certain forms of food compared with 24 per cent. of the other two groups.* It may be mentioned that this increased tendency to develop hypersensitivity is not due to the presence of a greater proportion of eczema cases in its composition, the figures for the ' summer,' ' winter ' and ' non-seasonal ' groups being 17, 18 and 22 per cent. respectively.

Enumeration of unusual causes of sensitization responsible for allergic symptoms is of scientific interest, but at the same time is of small value

* No effort was made to confirm this sensitivity to foods which was based purely on the mothers' observations.

in dealing with the average case of asthma. The frequency with which grass pollen acts as an allergen in asthma cases, however, apart from those with definite hay-fever, affords information of value in treatment of the condition. The figure of 42 per cent. for pollen sensitive cases compares with 60 per cent. for a series of the same age group tested with chicken feather extract in a comparable dilution (2 mgm. nitrogen per cent.). Pollen therefore may be placed with chicken feathers and horse hair as being one of the antigens to which exposure is almost universal, and to which a very high proportion of asthmatics are sensitive.

Just as the routine removal of feathers and hair containing materials from the environment of asthmatics is often accompanied by a very definite improvement in the frequency of attacks, so may avoidance of contact with pollen be of value. This is possible at all events as far as more intimate contact is concerned. Thus ' a day in the country ' is often followed by an attack which might not occur after ' a day at the sea.' Many parents who have moved from the town to the country for the benefit of the child's health, might have been warned that increased contact with pollen would probably be followed by an increase in the number of attacks during the summer months, and so be saved from disappointment. Pollen-sensitive cases are not uncommonly free from their symptoms if they go to the seaside during the pollen season, provided they choose a place where the prevailing wind comes off the sea. Such patients would be well advised to take their summer holidays in June or early July. Finally, in cases where the offending allergen is recognized, improvement and not uncommonly relief, at least temporary, does follow injection of increasing amounts of the substance in question. The fact that so few cases are sensitive to one allergen only, is apt to obscure this fact. The treatment of hay-fever with pollen extracts is on the whole successful. Treatment of pollen-sensitive asthmatics by injection of pollen extract with or without extracts of other common allergens is therefore a reasonable procedure which is likely to be followed by a decrease in the frequency and severity of attacks.

My thanks are due to the physicians to out-patients at the Hospital for Sick Children, Great Ormond Street, for allowing me to make use of their cases.

Conclusions.

1. Of two hundred and fifty children 42 per cent. gave positive intradermal reactions to grass pollen extract.

2. Of those whose symptoms were more intense during the summer months 61 per cent. are sensitive compared with 32 per cent. of the remainder.

3. Those cases who have or have had eczema give a higher proportion of reactors than any other group, except the occasional case whose asthma has developed after and apparently as a direct result of hay-fever.

4. Suggestions are made with regard to treatment.

IRON-DEFICIENCY ANAEMIA IN CHILDREN:
Its association with gastro-intestinal disease, achlorhydria and haemorrhage

BY

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This communication deals principally with the occurrence of iron-deficiency anaemia in children who have passed the period of infancy, in whom factors other than those commonly causing infantile nutritional anaemia have played a part. The common causes of nutritional anaemia have been classified by Mackay[13] and Parsons et al[19], and amongst these are some which may also affect older children; further facts concerning the causation of iron-deficiency anaemia after infancy, its relation to other morbid processes and its association with achlorhydria and chronic intestinal disease are now reported.

Haematological criteria of iron deficiency.—Since iron is essential for the formation of haemoglobin, failure of the organism to obtain a sufficient supply leads to diminished production of haemoglobin. The first stage in this is shown by a fall in the haemoglobin content of the cells. More serious degrees of iron deprivation result as well in a diminished output of erythrocytes, always proportionally less than the hypochromia, so that it is common to find that when the anaemia is severest the haemoglobin saturation of the cells is lowest. When iron therapy is instituted the following changes occur in the peripheral blood: first, a reticulocytosis, which reaches its maximum at the end of about a week and then with recovery, slowly falls to normal; secondly, a rise in the erythrocytes to slightly above normal; thirdly, a slow rise of haemoglobin to normal; and finally in some cases a slight reduction in the number of circulating red cells (Hagen's phenomenon). The changes in the diameter of the red cells have been shown to be the same in infantile nutritional anaemia[19] as those described by Price-Jones in the idiopathic microcytic anaemia of adults[21]; there is a microcytosis which diminishes with recovery, the process being accompanied by an increased variability while this is taking place. The diminution in mean corpuscular

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* In receipt of a grant from the Thomas Smythe Hughes Medical Research Fund.

volume observed by Vaughan and Goddard[23] has been noted in cases to be quoted in this paper. Since no other substance causing these changes, and resulting in the recovery of the anaemia, has been found, it is reasonable to assume that in cases of doubt the evoking of the response by iron therapy, reticulocytosis in particular, may be used in final confirmation of the diagnosis.

Other haematopoietic factors may be deficient as well as iron, and the response will then be incomplete; in cases where iron is not deficient, the response will be absent. It has been stated that iron, quite apart from its rôle as an integral part in the haemoglobin molecule, may act as an erythropoietic stimulant even although there is no deficiency[22]. We, ourselves, have not produced a reticulocytosis in normal infants with therapeutic doses of iron, though Barr[1] using massive doses claims to have done so.

Achlorhydria.

Though achlorhydria is recognized as a feature of idiopathic microcytic anaemia of adults, so that Witts[26] demonstrated either absence or extreme reduction of hydrochloric acid in the fractional test-meals of 81 per cent. of his series of adult women, yet investigators of the nutritional anaemia of infants have not so far attempted to establish any disorder of gastric function in their cases. Knowledge of the normal gastric function in infancy is incomplete, but in health, after four weeks, hydrochloric acid is secreted at all ages.[6, 7, 18, 14, 25, 17].

Recently we have begun to investigate the gastric function of cases of simple iron-deficiency anaemia by the method of the fractional (alcohol) test-meal. In twelve of thirteen successive patients, whose ages ranged from eight months to ten years, achlorhydria was found (see table 1).

TABLE 1.

TWELVE CASES OF IRON-DEFICIENCY ANAEMIA ASSOCIATED WITH ACHLORHYDRIA.

PATIENT.	AGE.	PRESUMED AETIOLOGICAL FACTORS.
*J. D. (Case 1)	8 months	Prematurity and possibly iron-deficiency in the mother.
*R. S. (Case 2)	13 months	Prematurity, malnutrition.
E. M.	15 months	Prematurity, malnutrition.
F. M.	19 months	Refusal of practically all foods except milk with consequent undernutrition.
A. P.	1 yr. 11 mth.	Breast fed 11 months, then dried milk 3 months: appetite always poor.
M. P. } Twins R. P. }	2 years	Twin-gestation.
W. S.	3 yr. 8 mth.	Had been on a mixed diet which may have been insufficient: history of haemorrhage after tonsillectomy some considerable time previously.
*T. H. (Case 3)	4 yr. 2 mth.	Home diet inadequate; anaemia appeared to have persisted on the diet of a hospital for infectious diseases (7 months).
R. K.	5 yr. 6 mth.	Diet inadequate since birth.
M. H.	6 years	Causation unknown: diet good.
*P. F. (Case 4)	9 yr. 6 mth.	Causation unknown: diet good.

* Case records follow.

In three cases achlorhydria was still present a year or more after cure by iron. Four of these twelve cases have been selected in illustration of the achlorhydria which may accompany iron-deficiency anaemia at various periods of childhood.

Case 1.—SIMPLE IRON-DEFICIENCY ANAEMIA ASSOCIATED WITH PERSISTING ACHLORHYDRIA.

J. D., a male aged eight months, was admitted for 'jaundice.' His mother had been treated for anaemia of some years' duration; the patient was a premature baby, weighing three lb. at birth. He was breast fed for one month and then given Nestle's milk and Cow and Gate. A week before admission, after a simple acute infection, a yellow pallor was noticed. On examination he was a well-nourished, pallid infant, with Harrison's sulcus, a 'rachitic type' head, enlarged spleen, no jaundice, and normal bone x-ray.

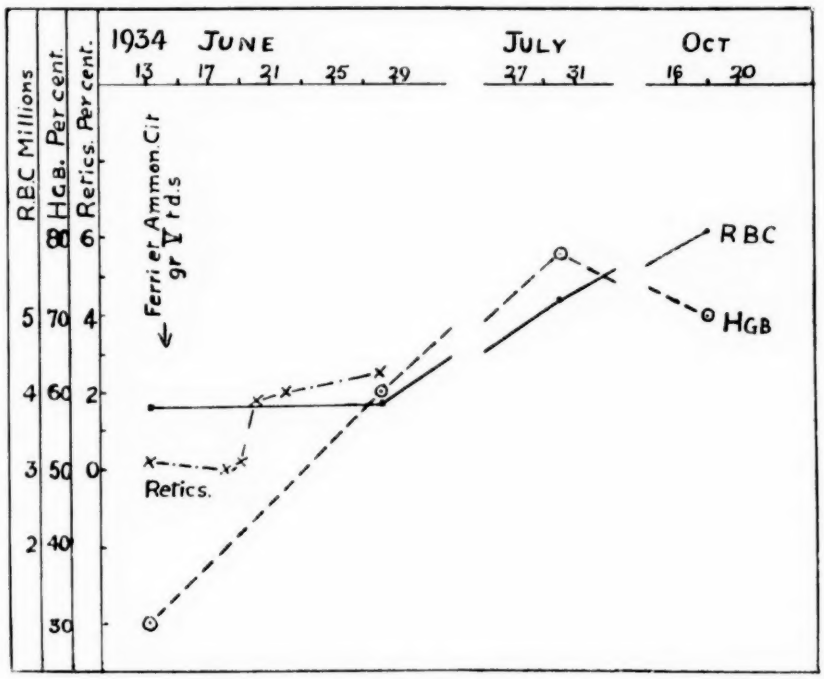

FIG. 1.—J. D.

Note : All haemoglobin investigations by Haldane's method.

GASTRIC ANALYSIS. An alcohol test-meal showed an absence of free hydrochloric acid.

SEQUEL. Adequate clinical improvement observed; gain in weight. Disappearance of splenomegaly. Achlorhydria still found after four months. Achlorhydria after injection of histamine (0·05 mgm.) was also observed in this case.

Case 2.—SIMPLE IRON-DEFICIENCY ANAEMIA ASSOCIATED WITH PERSISTING ACHLORHYDRIA.

R. S., a male aged thirteen months, was admitted to hospital for anaemia with a history of increasing pallor for two months. He was one month premature, birth weight six lb. He had been breast fed for three weeks, and then fed on diluted cow's milk until eight months old, followed by eight months of practically no solids, without gravy and green vegetables, but he received Robinson's Groats and stewed fruit in

addition to milk. He was a pallid child, yellow tinted, with the spleen not palpable and no jaundice.

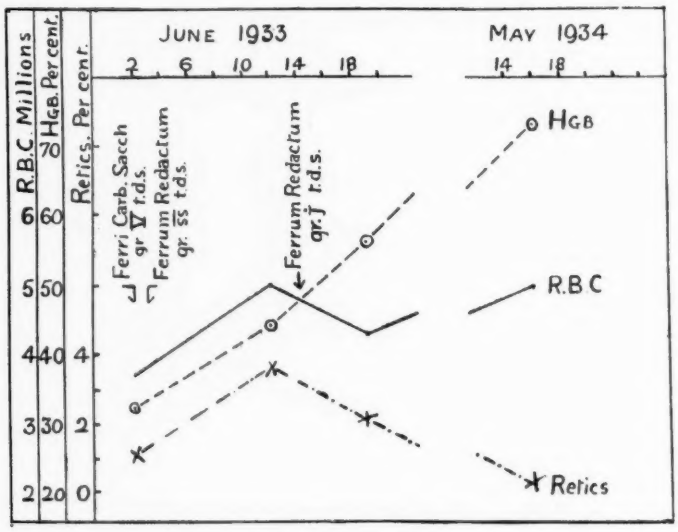

FIG. 2.—R. S.

The child was discharged before complete recovery had taken place.

GASTRIC ANALYSIS. An alcohol test-meal during his stay in hospital showed a complete absence of free hydrochloric acid.

SEQUEL. A year later there was no pallor, but on gastric analysis free hydrochloric acid was still absent and a Price-Jones curve showed a tendency to microcytosis (mean cell diameter 6·762μ).

Case 3.—IRON-DEFICIENCY ANAEMIA ASSOCIATED WITH POVERTY AND ACHLORHYDRIA. **T. H.**, a male aged four years and two months, was admitted to hospital for anaemia. The mother stated that he had always been pale and inadequately fed on

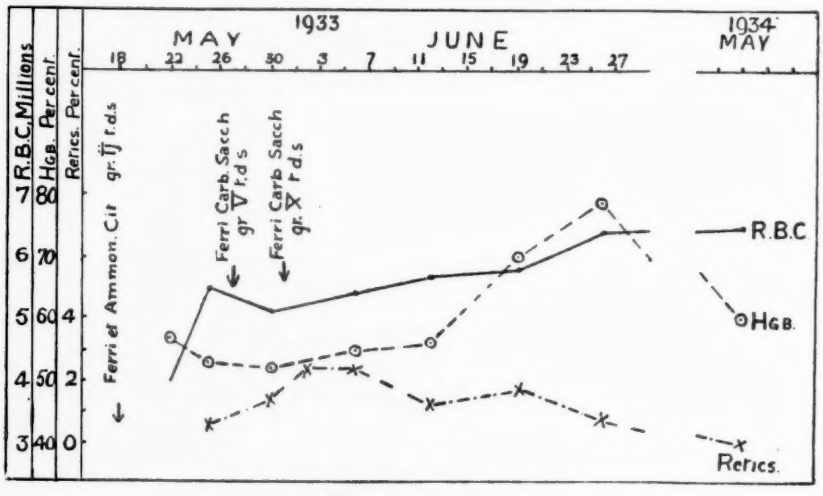

FIG. 3.—T. H.
14.5.34. Mean red cell diameter (Price-Jones) = 6·655μ.

account of poverty. He was breast fed for the first three months and then received dried milk. He had not ailed until he developed scarlet fever eight months before admission. He was in an isolation hospital for seven months and was then referred

to us by the London County Council. He was sallow with pale mucosae, thin and apathetic, with a slightly enlarged heart and a mitral systolic murmur widely propogated. The spleen was not palpable.

GASTRIC ANALYSIS. An alcohol test-meal during his stay in hospital showed a complete absence of free hydrochloric acid.

SEQUEL. A year after he came under observation he was re-examined. He was no longer pale, but was well-grown, with a slight degree of microcytic anaemia as shown by haemoglobin estimation and a Price-Jones curve (mean cell diameter 6·655μ). Gastric analysis showed that absence of free hydrochloric acid had persisted.

Case 4.—IRON-DEFICIENCY ANAEMIA WITH ACHLORHYDRIA TWO YEARS AFTER COMPLETE RECOVERY.

P. F., a female aged nine-and-a-half years, was admitted for the investigation of anaemia. She was born in India and breast fed for thirteen months, being brought to live in England at one year and nine months. She had a good home and good feeding. Pallor and languor had been present for six weeks. There was loss of appetite and disinclination for work or play. She was a well-grown child, mentally alert, with no wasting. Pallor of skin and mucous membranes was present with a haemic murmur at cardiac apex. The abdominal viscera were normal to palpation. She was treated first as an in-patient and subsequently at home, making a slow but complete recovery on a mixture containing ferri perchlor. ♏ v, with liquor arsenicalis hydrochlor. ♏ ij. A month after the beginning of treatment liver extract was introduced.

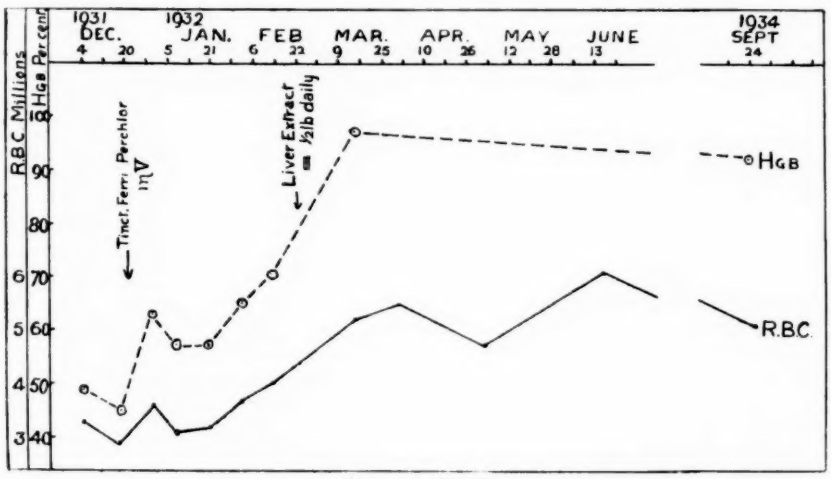

FIG. 4.—P. F.

SEQUEL. When re-examined two years after recovery there was no anaemia, but an alcohol test-meal demonstrated absence of free hydrochloric acid although she appeared to be in robust health.

Though the number of cases investigated by this method is small, we regard persistance of achlorhydria after apparent recovery as probably significant in the aetiology of the anaemia, especially in view of analogous findings in the idiopathic microcytic anaemia of adults. Confirmation of our findings needs to be obtained by similar observations in a larger series of cases and we are continuing to investigate patients by gastric analyses, employing histamine in some.

Anaemia associated with intestinal disease.

The following are two cases of anaemia in which an intestinal polypus was unexpectedly discovered at autopsy, no melaena having occurred to suggest the diagnosis. Are intestinal polypi and analogous conditions

too easily overlooked as causative lesions in certain cases resembling nutritional anaemia?

Case 5.—ANAEMIA WITH INTESTINAL POLYPUS AND INCOMPLETE RESPONSE ON IRON-THERAPY.

J. R., a female of ten months, was admitted for anaemia, bronchitis, and loss of weight. It was stated that she had always been pale, and that she had nearly died of bronchitis and pneumonia five weeks previously. Since this illness the anaemia had increased. Though she had been a full-time baby, breast fed throughout, she had gained weight slowly. She was a well-nourished, anaemic baby with a systolic cardiac murmur and the spleen was not enlarged. A week after admission diarrhoea and vomiting set in without naked-eye blood in stools. Subcutaneous salines were required to combat dehydration. Death from gastro-intestinal disorder took place four weeks after admission.

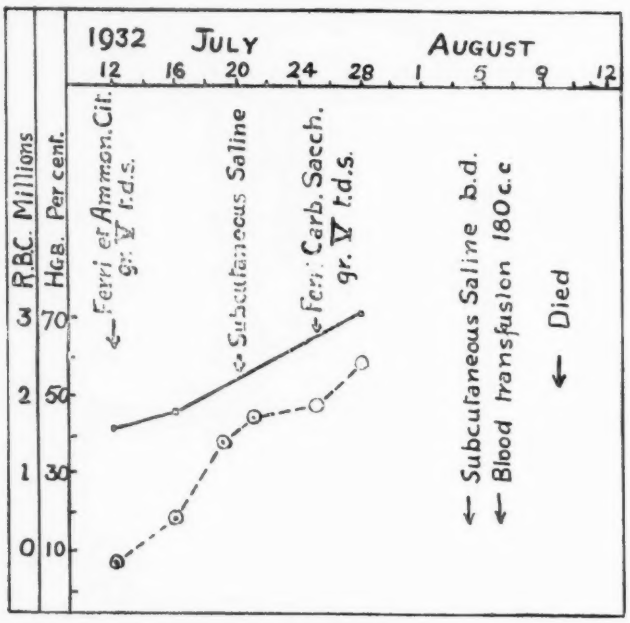

FIG. 5.—J. R.

POST MORTEM. The findings were those of anaemia and toxaemia, together with the discovery of a polypus in the small intestine; both middle ears contained pus. The tissues generally were pale; the heart was pale and dilated; the liver and kidneys were pale and fatty. In the small intestine, eight feet above the ileo-caecal valve, was a firm round polyp as big as a walnut, and covered with a rugose mucous membrane.

Case 6.—ANAEMIA WITH INTESTINAL POLYPUS AND CONGENITAL HEART DISEASE.

P. S., a female aged five years, was admitted for convulsions and congenital heart disease. A congenital heart lesion was recognized when she was five months old. Attacks of unconsciousness, preceded by abdominal pain, had occurred for a few months. She was a pale, well-nourished child, with congenital morbus cordis without cyanosis. The spleen was not palpable. Haematology: 21.1.33—R.B.C. 4·52 mill., Hgb. 63 per cent., reticulocytes 3·9 per cent. (eight days after beginning of iron-therapy). 30.1.33—R.B.C. 4·2 mill., Hgb. 72 per cent., reticulocytes 0·5 per cent.

SEQUEL. She was admitted to the East Ham Memorial Hospital ten months later, having, for a week, passed large quantities of blood per rectum. A blood transfusion of 300 c.c. was given; despite this she died.

POST MORTEM. A large ulcerated pedunculated polypus was found in the sigmoid colon, and a patent ductus arteriosus was present.

In each of these cases ordinary iron-deficiency anaemia was diagnosed and this opinion was supported when on iron therapy a haematological response was seen. Nevertheless, recovery was not obtained perhaps, in one case at least, because occult haemorrhage continued from a polypus the presence of which had not been suspected during life. Conditions other than polypus, by producing long-continued occult haemorrhage, are known to result in an anaemia which responds to iron. In ulcerative colitis for example a similar anaemia may be observed, partly due to haemorrhage, sometimes manifest as melaena.

Case 7.—SEVERE ANAEMIA RESPONDING TO IRON AND BLOOD TRANSFUSION, ASSOCIATED WITH ULCERATIVE COLITIS.

D. B., a male aged two years and nine months, was admitted for ' colitis and melaena.' Nine weeks previously bouts of illness had begun in which he passed blood and slime. The stools were about six a day. He was well-nourished, pale, with a haemic murmur, and no enlargement of spleen. All investigations as to aetiology of ' colitis ' were negative. He was readmitted at the age of three years and eleven months on account of a relapse of symptoms, worse than on the previous occasion having passed fifteen stools, mostly blood. In addition to medical treatment he received a whole blood transfusion of 360 c.c. with beneficial results. Readmitted aged four years and eight months, after numerous relapses the patient showed a further response to medical treatment which was very slow and relapses occurred. Blood transfusions seemed beneficial. He was readmitted aged five years and one month for severe secondary anaemia. The patient appeared palid and apathetic, with fair nutrition, and having diarrhoea with blood and mucus. The anaemia responded to iron therapy, the haemoglobin rising from thirteen to fifty-eight per cent. (fig. 6). At this stage relapses due to further haemorrhage occurred necessitating subsequent transfusion; eventually a haemoglobin reading of 70 per cent. was reached.

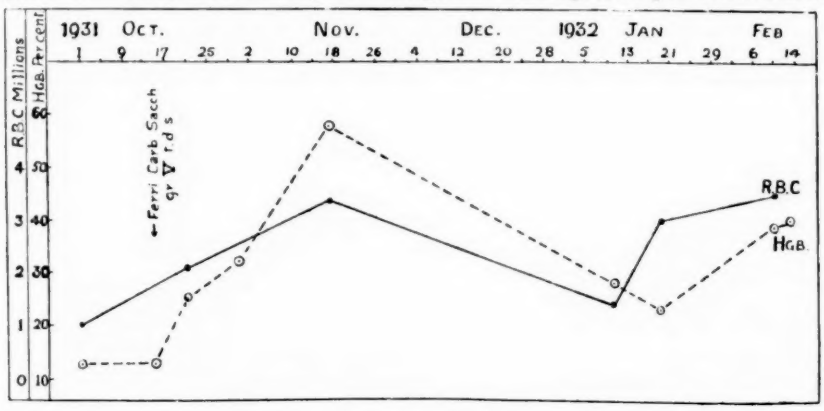

FIG. 6.—D. B.

Instances of so-called ' ulcerative colitis ' such as the one just described illustrate the fact that any given anaemia may have its cause in a number of circumstances. Contributing to the iron-deficiency discovered in this child were factors such as the invalid diet used in the treatment of his complaint, the intestinal lesions and chronic diarrhoea which probably hindered intestinal absorption, and also the long-continued intestinal bleeding so characteristic of the condition. It may be noted that our knowledge of the pathology of similar cases of intestinal haemorrhage is unsatisfactory. In the present instance the source of the bleeding was not located.

Coeliac disease.

Intestinal factors are known to play the leading part in the anaemia of coeliac disease. Iron deficiency is commonly present, and results in a microcytic type. Megalocytic anaemias[10, 24, 12, 3] responding to liver and marmite have been recognized, particularly in the older cases. The following cases were characterized by severe hypochromic anaemia, but not by achlorhydria.

Case 8.—SEVERE ANAEMIA ASSOCIATED WITH COELIAC DISEASE.

E. W., a male aged seven years, was admitted for abdominal pain and vomiting, having been ' yellowish ' for six months. He was the third in a family of four, an elder sister having also suffered from coeliac disease. (This sister was also admitted and the diagnosis confirmed.) Abdominal pain and vomiting had occurred in attacks for a period of two years. He had been anaemic and apathetic for six months, the bowels being constipated except during attacks, when the stools were light, loose and offensive. He showed great asthenia with dark pigmentation of scars and exposed areas of which the cause was not explained. The spleen was enlarged. The van den Bergh reaction was normal. A stool contained split fat 62·4 per cent., unsplit fat 3·95 per cent., total fat 66·43 per cent. Microscopically, large excess of fatty acid crystals were found.

TABLE 2.

DATE.	R.B.C. (MILLIONS PER C.MM.).	HAEMOGLOBIN PER CENT. (HALDANE).	COLOUR INDEX.	RETICULOCYTES (PER CENT. OF R.B.C.)	W.B.C. PER C.MM.	TREATMENT.	NOTES.
4.8.32	1·81	46	1·29	—	6,200		An; Poik; Poly; 1 Normoblast / 100 W.B.C.
10.8.32	2·59	31	0·62	—	—		Platelets: 82,900 / c.mm.
16.8.32	—	—	—	0	—		Poik; An; Poly; P.B.;
19.8.32	—	—	—	0	—	Pulv. Ferri Carb. Sacch. gr. v t.d.s.	Poik; An;
20.8.32	—	—	—	1·3	—		
22.8.32	1·80	44	1·25	3·4	5,000		An; Poik; 1 Normoblast / 100 W.B.C.
23.8.32	—	—	—	7·5	—		
24.8.32	—	—	—	3·9	—		Price-Jones' Curve—Mean Cell Diameter 7·3235 μ
25.8.32	—	—	—	1·4	—		
8.9.32	3·50	57	0·71	0	6,500	Pulv. Ferri Carb. Sacch. gr. xx t.d.s.	1 Normoblast / 100 W.B.C.
2.10.32	—	—	—	—	—		Price-Jones' Curve—Mean Cell Diameter 7·354 μ
12.1.33	4·50	61	0·67	—	7,000		
22.2.33	4·70	64	0·68	—	—		
21.8.33	5·60	68	0·60	—	7,400		
20.10.33	4·80	71	0·73	0·5	10,400		

An. = Anisocytosis.
Poik. = Poikilocytosis.
Poly. = Polychromasia.
P.B. = Punctate basophilia.

GASTRIC ANALYSIS. An alcohol test-meal showed figures within the limits of normal acidity.

SEQUEL. He received orthodox treatment for coeliac disease over a long period in the country branch hospital at Tadworth, and behaved in the manner characteristic of his disorder.

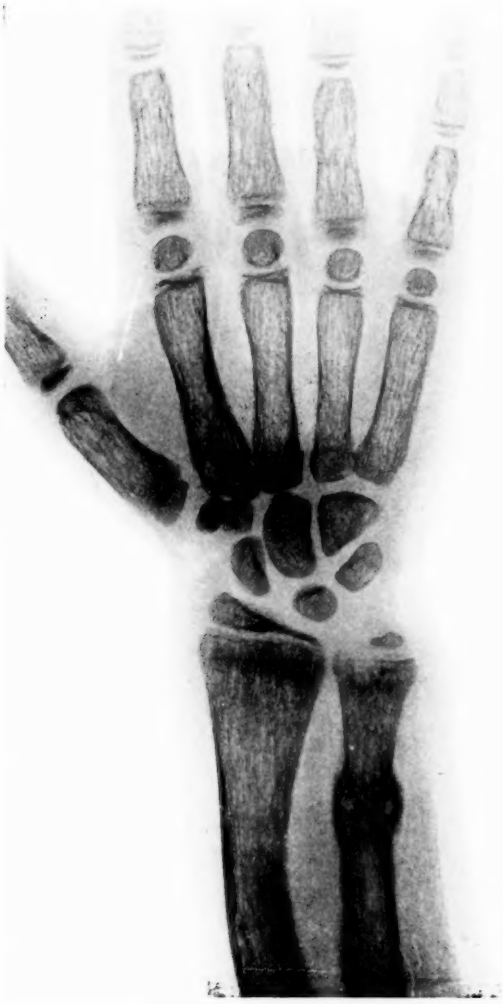

FIG. 7.—Coeliac rickets, osteoporosis, healing (spontaneous) fractures. (Case 9.)

Case 9.—SEVERE ANAEMIA WITH COELIAC DISEASE AND RICKETS.

K. A., a female aged twelve years when first admitted to hospital for coeliac disease. She weighed only three lb. at birth and was physically backward during infancy. Until four-and-a-half years ago her health was stated to be good. Since that time she had been subject to attacks of vomiting of a week's duration and abdominal pain. The stools had often been pale, loose and frequent, though she had

also had periods of constipation. The symptoms had been growing worse for the last six months and her legs had been weak, so that she required to be carried up and down stairs. She was anaemic and stunted. Her height was 42 in. (average at twelve years being 57 in.); her weight was 35 lb. (average weight at twelve years being 81 lb). Radiological examination showed numerous spontaneous fractures in various stages of healing, and ricketty changes in the epiphyses (fig. 7). The blood serum calcium was 6·6 mgm. per cent. (normal 9 to 11), and the inorganic blood phosphorus 2·9 mgm. per cent. (normal 4 to 5·5). The stools were greasy and their analysis showed:—split fat 47·2 per cent., unsplit fat 18·1 per cent., total fat 65·3 per cent.

GASTRIC ANALYSIS. An alcohol test-meal demonstrated the presence of small amounts of free hydrochloric acid during the first twenty minutes but not subsequently. Orthodox treatment for coeliac disease was instituted. She improved very gradually, and gained weight, the total fat in the stool eventually falling to 42·8 per cent. The response to haematological treatment is shewn in fig. 8. Iron

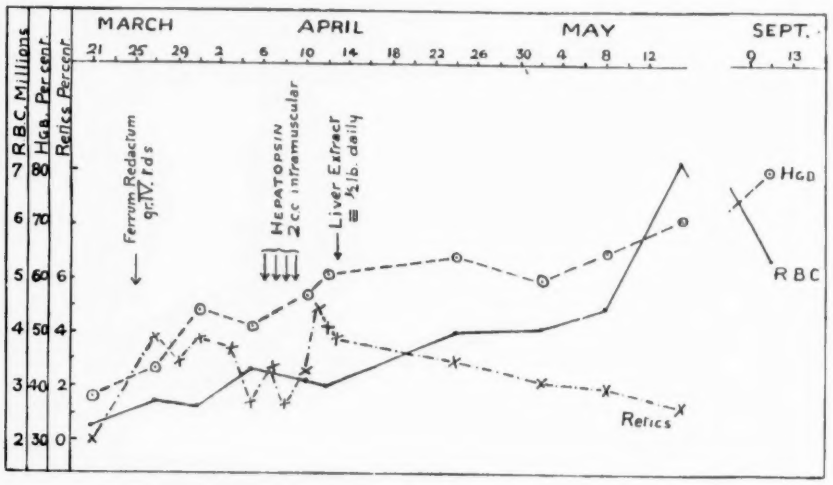

FIG. 8.—K. A.

therapy raised the haemoglobin from 30 per cent. to 54 per cent. and then recovery was checked until hepatopsin (intramuscular), and later liver extract, were employed. Eventually complete restitution of the blood picture was seen.

Anaemia associated with other diseases.

In a great number of other diseases iron deficiencies may arise. We have seen haemolytic anaemias of various types show a latent iron deficiency unmasked during their recovery. This may occur, for example, in the haemolytic anaemias of the neontal period[11], in Lederer's anaemia[20], von Jaksch's anaemia, and also in splenic anaemia[9] and we have seen the characteristic response to iron in some cases of anaemia accompanying congenital syphilis, rickets and cardiac rheumatism.

Discussion.

In the aetiology of the nutritional anaemia of infancy, which we prefer to call iron-deficiency anaemia, factors such as prematurity, twin-gestation, hypochromic anaemia in the mother, over-prolonged milk feeding and defective diet, are well recognized. Though its clinical appearance may be similar, the analogous iron-deficient state seen after the age of infancy would appear to have a somewhat different background. Often the anaemic aspect forms part of the clinical picture of some chronic condition; more occasionally it may be seen in an acute disease, particularly when treated by strict diet or associated with much anorexia. Gastro-intestinal disorders would appear to be more directly related, and we have shown that achlorhydria may be a causal factor. It may be questioned whether the achlorhydria which we have demonstrated in certain cases was post hoc or propter hoc, and indeed the same point was raised, and settled, concerning the adult cases of idiopathic microcytic anaemia[26]. The persistence of the achlorhydria after successful treatment of the anaemia and the tendency to anaemic relapses have been taken as evidence that the acid deficiency is not secondary to the anaemia. We have proved the persistence of acid deficiency in those of our achlorhydric patients who have been cured for a year or more. Iron absorption is held to depend largely on the activity of the acid gastric secretion which converts food-iron into ferric and ferrous chlorides[8]. The conditions for absorption of these salts are at their optimum in the duodenum when its contents are acid[15]. The secretion of hydrochloric acid is not essential for the absorption of iron and increased ingestion of iron may make up for an acid deficiency. This provides the explanation for the clinical success of adequate iron therapy. Nevertheless, achlorhydria is probably as much an indication for the use of hydrochloric acid as an adjuvant in the iron-deficiency anaemias of childhood as it is in those of the adult.

With regard to the iron-deficient states seen in infants, there are still problems of causation which await solution. For example, not all cases of nutritional anaemia are to be satisfactorily explained by the recognized causative factors mentioned above. From time to time anaemic infants are encountered who have been born of healthy mothers, at full time, breast-fed and remain outwardly free of disease. Such cases led Czerny to postulate a constitutional anomaly by which he also explained the fact that, of two infants under similar conditions, one might develop an anaemia and the other not. This standpoint was supported by Kleinschmidt and others under designations such as ' hereditary predisposition ' and ' functional weakness of the blood-forming organs.' Mackay[13] finds these explanations inadequate on the one hand and vague on the other, and for these anomalies prefers to postulate the possibility of deficient iron-storage in the liver,

wasteful utilization, or even some unknown controlling factor comparable with calciferol in the metabolism of calcium and phosphorus. The position may be simplified by considering the physiology of iron-absorption in these cases.

Numerous observations on the gastric acidity of infants have shown that the pH may be expected to vary during digestion according to the nature of the feed, and the health and growth of the infant. Undernutrition and most forms of illness, particularly those of an infective nature, are commonly accompanied by a lowered acidity[6, 14, 18] and in infancy the total average volume of secretion is remarkably small in comparison with that found at later ages of childhood[17].

Under experimental conditions, Bauer[2] showed that gastric juice dissolves iron and that the amount dissolved varies with the pH. Further, Mettier and Minot[16] have supplied clear evidence that acid assists in the absorption of iron. The large doses of inorganic iron salts required for the cure of iron-deficiency anaemia in achlorhydric persons suggest that human subjects are physiologically economical with their food-iron by virtue of secretion of hydrochloric acid in sufficient quantity. It is even possible that for ordinary physiological requirements ferrous chloride is the only form of iron which is absorbed. In practice achlorhydria, and hypochlorhydria in less degree, may unmask a relative shortage of iron-intake, and vice versa.

It has been shown that minor degrees of iron-deficiency anaemia are common in infants both breast- and bottle-fed[13]. Setting aside natal and prenatal causes, such as prematurity, twin-gestation, etc., it has been found that this deficiency anaemia is more common, and usually more severe, in artificially-fed than in breast-fed infants. Differences in the pH of the gastric contents of infants digesting breast and cow's milk have been established by Marriott and Davidson[14], who found that infants fed on cow's milk had a higher average pH (lower acidity) due to the ' buffer effect ' of cow's milk protein. Compared with breast-milk feeding they found that the effective concentration of acid was less than one-twentieth. These results were later confirmed by the figures which Wills and Paterson[25] reported. In this fact is an explanation of Blauberg's[4] observation that iron retention is less on cow's milk than on human milk. When it is recalled that the iron content of cow's milk is less than that of human milk [cow's milk 0·00024 per cent. (Peterson and Elvehjem), human milk 0·0003 per cent. (Dorlencourt and Calugareanu-Nandris[13])] we have another reason why anaemia is relatively more common with cow's milk feeding, though it is doubtful if the difference in iron content is sufficient explanation to serve alone; indeed it is likely that the question of percentage retention is the more important. Certain other facts, such as the occurrence of anaemia in otherwise normal and breast-fed infants, may be accounted for by individual differences in percentage-absorption, as hinted by Mackay, and particularly in gastric-secretion, as suggested by this paper.

Summary.

The relation between acid deficiency during digestion and the occurrence of iron-deficiency anaemia is discussed, first, in children past the age of infancy, and secondly, in infants. Cases illustrating the achlorhyria which may be found in association with this type of anaemia are briefly described. Of the many gastro-intestinal disorders besides achlorhydria which may contribute to anaemia in children examples are reported of intestinal polypus, of so-called ' ulcerative colitis,' and coeliac disease.

Severe and apparently causeless anaemias, which respond wholly or partially to iron therapy, demand attention to the state of the gastro-intestinal tract. Haemorrhage from the intestine, sometimes occult, sometimes manifest, and digestive, as well as absorptive failures, may each present themselves in the guise of severe anaemia.

We are indebted to the Honorary Staff of the Hospital for Sick Children for allowing us facilities in investigating and publishing their cases, to Dr. David Nabarro as director of the Pathological Department, to Drs. Donald Bateman and R. H. Bailey for assistance with cases investigated at the Westminster Hospital, and to the Medical Research Council for an expenses grant.

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THE RELAPSE IN SCARLET FEVER

BY

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In this country during the past decade the prevalence of a benign type of scarlet fever has been reflected in the case mortality which has seldom exceeded one per cent. in any of the great cities. The present day chances of a severe attack of the disease may be illustrated by the statement that of 1,743 admissions to the Leeds City Hospital in 1933, only one manifested the malignant type, while twenty-three were examples of the septic type. In many parts of the country, isolation of a large proportion of cases of scarlet fever is still the normal practice. It is not intended within the scope of this paper to criticize this policy, but it is proposed to draw attention to a problem which may arise when an epidemic of benign scarlet fever is prevalent and isolation accommodation is consequently strained. The problem is that of the relapse.

The development of immunity to the disease is the normal expectation after an attack of scarlet fever. That this is not invariable is shown by the occurrence of second attacks and relapses. Second attacks, developing some months or years after the first attack, are according to Rolleston[1] more uncommon than relapses, yet it is noteworthy that, of the admissions to the Leeds City Hospital in 1933, 3·5 per cent. gave a history of a previous attack. As regards relapses the same authority, after making allowance for errors in the original diagnosis, estimates that a return of all the characteristic symptoms of the disease occurs in about one per cent. of all cases. The relapse rates for the Leeds City Hospital for the years 1931, 1932 and 1933, were 3·6, 4·0, and 4·3 per cent. respectively. Such rates appear to be high and they give rise to an administrative problem, as they indicate an additional burden on the available accommodation of the hospital and a definite increase in the cost of treatment of scarlet fever.

TABLE 1.

TIME OF OCCURRENCE OF RELAPSES.

	1931.	1932.	1933.	Total
First week	—	1	1	2
Second ,, ...	12	7	4	23
Third ,, ...	12	12	14	38
Fourth ,, ...	11	10	25	46
Later	17	8	26	51
Total ...	52	38	70	160

The time of occurrence of the relapses is noted in table 1. It will be observed that two relapses are recorded to have taken place in the first week and twenty-three in the second. The writer is aware that criticism may be directed to the original diagnosis of scarlet fever in these cases. It may be stated, however, that no case has been included in which there was not reasonable evidence in support of the original diagnosis at the time of admission of the patient.

It is generally accepted that the Dick test furnishes an indication of susceptibility or immunity to scarlet fever. In the first three days of the disease, over 70 per cent. of patients give a positive reaction. This is probably an under-statement, as Zingher[2] reports 93 and 100 per cent. in different series, and Joe[3] reports 95 per cent. The latter, however, states that he was using a toxin selected from others on account of its sensitiveness. As a result of the gradual development of immunity owing to the stimulus of the disease, the reaction tends to become negative by the end of the third week in the majority of patients. In the work of Zingher, to which reference has already been made, a reversal of the positive Dick reaction in the early stage to a negative in convalescence was noted in the whole of the 93 per cent., while in Joe's work, the 95 per cent. was reduced to about 5 per cent. after the thirtieth day. In contrast to these ideal results, it should be noted that in a later series of patients James, Joe and Swyer[4] gave a percentage of 57 in whom the reaction was still positive on the twenty-eighth day and after. The difficulties in the standardization of scarlet fever toxin appear to be responsible for these discrepant results.

An examination of the records of Dick tests in scarlet fever patients in the Leeds City Hospital in 1933 shows that positive reactions persisting to the end of the third week have been frequent. The conclusion appears to be unavoidable that the present benign type of scarlet fever provides in many cases insufficient stimulus for the development of immunity. Table 2 gives the details of Dick tests in 1,592 patients. As far as circumstances permitted, tests were performed on admission and again on approximately the twenty-

TABLE 2.

DICK TEST RESULTS IN RELATION TO RELAPSES.

1933.	Number of patients.	Number of relapses.	Percentage of relapses.
Dick test positive on admission			
Positive at end of third week	301	27	8·9
Negative ,, ,, ,, ,, ,, ...	241	2	0·8
Not tested later	238	14	5·8
Dick test negative on admission	435	4	0·9
Dick test recorded only in convalescence			
Negative	56	1	1·7
No record	321	22	6·8
Total ...	1,592	70	4·3

first day of the disease. The large number of negative reactors on admission includes a considerable proportion of late admissions to hospital. The majority of the patients tested in convalescence only were also admitted late in the disease. The patients of whom records are not available include, among others, serum-treated cases and cases in whom the reading of the Dick test was recorded as doubtful owing to the brightness of the rash.

With regard to the incidence of relapses in patients treated with scarlatinal antitoxin, Rolleston[1] records that he met no example in a series of over 350 cases selected for their severity. Burton and Balmain[5], on the other hand, recorded eighteen relapses (4·16 per cent.) among 432 consecutive cases of scarlet fever treated with scarlatinal antitoxin. Their total may be presumed to include many mild cases in whom the stimulus of the primary attack may have been insufficient to produce immunity. In Leeds it has been the practice to reserve antitoxin for the more acute cases. During the period 1931 to 1933, 208 patients received antitoxin. Intravenous administration was employed in 107 cases, the route in the remainder being intramuscular. Of the serum-treated cases, only four relapsed (1·9 per cent.), and these received the antitoxin intramuscularly. As might be expected, these relapses occurred rather late in the course of the disease and presumably after the antitoxin had been eliminated, the time of occurrence being the eighteenth, twenty-seventh, thirty-fourth and thirty-sixth days. It is of interest to note that while the relapse rate for 208 serum-treated cases was 1·9 per cent., the rate for 3,619 non-serum-treated cases was 5·6 per cent. As the average severity of the disease differed in the two groups, no inference can be drawn as to the effect of the antitoxin on the relapse rate, and it should be borne in mind that Burton and Balmain[5] have recorded a relapse rate of 4·16 per cent. for consecutive antitoxin-treated cases.

The possibility of a high relapse rate in benign scarlet fever creates a problem which demands attention. It may be suggested that the solution lies in the reduction of the period of isolation. Banks[6] advocates and practices the intravenous administration of antitoxin to all cases, and the discharge from hospital in a little over a fortnight. As most relapsing cases are probably reinfected while under treatment in hospital, this procedure would undoubtedly cut down the relapse rate, but the policy of administering antitoxin by the intravenous route to admittedly benign cases has not met with general approval. Few local authorities which attempt the hospitalization of scarlet fever on a large scale have cut down the period of isolation to less than four weeks, and in hospitals there is a tendency to accept the relapse with the same equanimity with which a ' return ' case is accepted. The isolation of patients in whom the transition of the Dick test from positive to negative fails to take place may be suggesed and is, indeed, frequently carried out, but in epidemic times this becomes impossible owing to the lack of accommodation. The solution of the relapse problem advocated here assumes the inadequacy of the primary stimulus at the onset of the disease. The stimulus is increased therefore and maintained by the administration of

prophylactic scarlatinal toxin. The procedure adopted in the Leeds City Hospital is as follows:—

All patients, to whom the administration of antitoxin is not indicated, are Dick tested on admission to hospital. To all positive reactors a course of graduated doses of prophylactic toxin is given, the course beginning as soon as the temperature has fallen to normal. Injections of 500, 2,000, 5,000 and 20,000 skin doses are given at four day intervals. Thus the course is completed before the end of the third week when the patient is allowed up, at which stage the risks of reinfection tend to increase. The injections are well tolerated and do not appear to have the slightest adverse effect upon the disease. The procedure was tried out for some months in a double ward to which children under five years of age were admitted. Table 3 gives the details.

TABLE 3.

THE EFFECT OF PROPHYLACTIC TOXIN ON THE OCCURRENCE OF RELAPSES.

	Number of admissions.		Number of relapses.		Number of patients receiving toxin injections.	
	A	B	A	B	A	B
1933						
July	33	113	3	—		
August	48	108	1	4		
September	65	222	1	2		
October	56	306	12	8	10	—
November	70	290	2	12	59	—
December	59	254	—	7	36	—
1934						
January	36	230	—	9	28	1
February	33	118	—	5	16	5
March	38	152	1	5	33	10
April	47	160	—	5	40	8

Note: A—Ward receiving children under 5 years of age.

B—Other wards.

It should be noted that the toxin injections were commenced on October 30, 1933, with new admissions only, so that the procedure could not affect the occurrence of relapses until November. Although the results appeared to justify the extension of the treatment to other wards, it was decided to continue the administration of toxin as a routine in the infants' ward only, and to employ it in selected cases in the other wards, so that the other wards might continue to act as a control. During a period of six months, it may be stated that only one relapse has occurred in the infants' ward. In this case, the Dick test was recorded as ' pseudo and negative ' on admission, in consequence of which the child did not receive toxin injections. Further, it is of interest to note that of 246 patients shown in table 3 as receiving toxin injections, only one relapsed. This patient was in a ward for older children where few had received toxin injections, and the relapse occurred thirty-five days after the last injection.

Conclusions.

1. The benign type of scarlet fever at present prevalent in this country frequently fails to produce immunity in the individual.

2. As a result second attacks and relapses may be more common.

3. The prevention of relapses is sound economy and is beneficial to the individual.

4. The administration of scarlatinal toxin is suggested as a logical procedure in the prevention of relapses.

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